REMARKS

I. Claims in the Case

Claims 1-53 and 120-129 have been cancelled. Claims 131-141 have been added. Claims 54-60 and 131-141 are under examination. Claims 61-119 and 130 stand withdrawn from consideration.

Support for the broadening amendment to claim 54 can be found in the specification at page 5, liens 1-3.

Support for the new claims 131-132 can be found at page 80, lines 14 and 17. Support for the subject matter of new claims 133-136 can be found in Table 2 at page 83.

Support for new claim 138 and 141 can be found on page 5, lines 1-3, and Example 1 and Table 2 (page 83).

Support for new claims 139-140 can be found on page 6, lines 1-2.

II. Rejections Under 35 U.S.C. §112, Second Paragraph

Claim 58 was rejected as depending from itself. The claim has been amended to correct the dependency. The Examiner's assistance is appreciated.

III. Rejections Under 35 U.S.C. §103

All of the claims have been rejected over Mehta in view of Ulukaya (claims 54-56) or in view of Minton or Zeligs (claims 54-60). The Action takes the position that Mehta teaches liposomal formulations of retinoids in combination with DMPC and soybean oil. Ulukaya is cited as teaching that 4-hydroxypheyl retinamide (4-HPR) has various advantages over naturally occurring retinoids, including fewer side effects. Minton and Zeligs are cited as teaching other advantages to 4-HPR.

In response, Applicants would first note that, at best, the prior art of Mehta only renders it "obvious to try" to produce lipid formulations of other retinoids, which is not an appropriate standard for demonstrating statutory obviousness. Second, it is Applicants' position that none of the secondary references provides a specific motivation to combine with the teachings of Mehta. For example, Ulukaya contains no disclosure that Applicants can find that suggests a liposomal formulation, and the Examiner appears to concede this and simply relies on supposed advantages of 4-HPR *per se*. However, it is unclear how this fact alone provides a suggestion to provide the 4-HPR in the lipid formulation of Mehta. Indeed, there is evidence in Ulukaya that teaches away from the combination: Ulukaya teaches that 4-HPR has properties that distinguish it from naturally occurring retinoids, including the fact that it apparently exerts its clinical effects by a different pathway from classical retinoids. This fact suggests that 4-HPR has *different* physicochemical and/or biological properties from classical retinoids, which immediately brings into question whether one of ordinary skill would have an expectation that this very different retinoid could be practiced in the context of the teachings of Mehta. We think not. Furthermore, with the known advantages described in Ulukaya, we question whether one of skill would be motivated to try to modify it in any way. Again, we think not. Lastly, we would point out that Mehta proposes the use of lipid formulations is for the purpose of "reduced toxicity" (col. 2, lns 57-58), yet Ulukaya teaches that the 4-HPR in and of itself solves the toxicity problem, finding that it was well tolerated in patients – so again, there is no motivation from Uluyaka or Mehta to provide a lipid based formulation of 4-HPR.

The Minton reference is said to teach sustained or continuous release formulations, but it is hard to see how this disclosure is relevant to DMPC/SO/water formulations of 4-HPR and the Examiner has not provided any explanation in this regard. On the contrary, Minton simply

teaches that one can prepare sustained release formulations of the 4-HPR and calcium glucarate. However, it is hard to imagine how the preparation of a sustained release formulation of these two drugs would lead one of skill in the art to Mehta – as noted above, Mehta is concerned with formulations having reduced toxicity and appears to teach that one can administer liposomal retinoids for longer periods of time without toxicity (see, *e.g.*, col. 4). Perhaps Applicants have missed the teachings that the Examiner is relying upon. So, if the Examiner is aware of some teaching in Mehta that its liposomal retinoid formulations are for the purpose of providing a sustained release formulation, the Examiner is requested to identify the teaching relied upon on the record. (Applicants have on-line searched the Mehta patent for the word "sustained" without success, and have only found the word "continuous" in relation to continuous therapy with retinoids as opposed to teaching that the lipid formulations provide this benefit.)

Zeligs is the one reference that does refer generically to liposomal forumations of DHEA and retinoids such as 4-HPR, but again, there is no basis for combining this teaching with Mehta *per se* to arrive at the presently claimed invention. In particular, it is noted that Zeligs is primarily concerned with topical therapy and topical compositions for the treatment of skin disorders and for protection against UV light. There is some disclosure that concerns parenteral administration – indeed, liposomal formulations are only mentioned in the context of systemic administration (col. 6, ln 60). While no specific indications for liposomal formulations *per se* are given by Zeligs (see col. 6, ln 60), there is disclosure that systemic administration is to "prevent" the "recurrence" of squamous cell carcinoma. Furthermore, there is no disclosure that would, in the Applicants' opinion, suggest to one of skill in the art to select and use a DMPC/SO/water formulations – certainly a very general disclosure such as Zeligs (which only appears to mention

the word "liposome" once) cannot render each and every cancer therapeutic methods suing lipid formulations obvious. There must be more.

We would further point out with respect to Zelig that the only phospholipid formulation it discloses, which appears to be a lipid emulsion, is for topical or ophthalmic application and is described beginning at col. 10, line 53. Moreover, in addition to this formulation being only for topical/ophthalmic application, it also comprises an *extremely* low ratio of retinoic acid (RA) to lipid (50 mg RA as compared to 700 mg phospholipid and about 0.6 g octanoic acid,[1] which provides a ratio of about 1:26), well outside of the ratios set forth in dependent claims 133-136.

Furthermore, Applicants' specification demonstrates that DMPC/SO/water formulations of 4-HPR has surprising advantages over the liposomal formulations of prior retinoids shown in Mehta, and that these advantages are totally unrelated to the known advantages of 4-HPR. IN particular, the Examiner's attention is directed to the incorporation efficiency studies shown in Table 2, page 83, of the specification. Here it is seen that the incorporation efficiency 4-HPR in liposomes of DMPC and SO is surprisingly high, most above 80% and two in the 90% range. In contrast, the incorporation efficiency of, for example, retinoic acid in liposomes is, in most instances, substantially lower (see Table 1 of Mehta, at col. 8) – most beign in the range of about 50-70%. The only exceptions to this are in the case of DMPC:DMPG liposomes. However, DMPG is taught to have "undesirable effects" and other problems/shortcomings (see Mehta, col. 6, lines 43-54). Thus, the lipid formulated 4-HPR of the present invention is able to achieve incorporation efficiencies consistent with the highest levels shown in Mehta, while avoiding the inclusion of undesireable lipids such as DMPG.

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[1] We have calculated that 0.7 mls of octanoic acid has a weight of approximately 0.6 g)

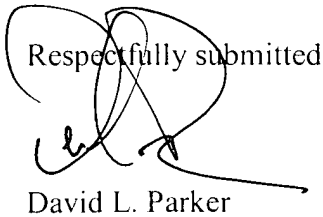
Regarding certain particular embodiments (see, e.g., claims 138-141), we have been unable to identify any teaching in Mehta that concerns lipid formulations of retinoids that are encapsulated in a lipid material that contains water. While Mehta does disclose reconstitution of already formed liposomes in an aqueous solution (see, *e.g.*, col. 7, ln 66, to col. 8, ln 3) it does not appear that there is any teaching of actually forming the liposome using water with the lipids. For example, the technique disclosed by Mehta in example 1 does not appear to involve the use of water (see col. 7, lns 54-64). Applicants have been unable to identify any relevant teaching from Mehta, but would appreciate it if the Examiner could review the specification as well as it is always possible that we have missed something.

In contrast, our specification, in Table 2 at page 83, clearly discloses the preparation of lipid compositions of 4-HPR/DMPC/water and 4-HPR/DMPC/SO/water. Importantly, the incorporation efficiency of these two formulations were quite high (ranging from 77.5 to 96.4, with the average being 87.3%). However, in the formulation shown in Table 2 without water, the incorporation efficiency was dramatically lower – only 60%! This is even more surprising in that 4-HPR is a lipophilic drug – one would have more likely have predicted that a lipophilic drug would not incorporate as readily and efficiently in liposomes prepared using water.

Thus, for the foregoing reasons, it is respectfully submitted that the Examiner has failed to make a *prima facie* case of obviousness and that the invention is shown to be surprising unexpected in light of the prior art.

The Examiner is invited to contact the undersigned attorney at (512) 536-3055 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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